Medical Policy

BlueCross BlueShield of Kansas
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Title: Positron Emission Tomography (PET) Scanning: In Oncology to Detect Early Response during Treatment

See also: Positron Emission Tomography (PET) Scanning: Cardiac Applications
Positron Emission Tomography (PET) Scanning: Oncologic Applications
Positron Emission Tomography (PET) Scanning: Miscellaneous (Non-cardiac, Non-oncologic) Applications

Professional
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DESCRIPTION

Positron emission tomography (PET) scan has many established roles in oncology. Another potential use of PET scanning is early in the course of treatment to assess treatment response, with the intent of altering therapy if the PET scan shows inadequate response.

Positron emission tomography (PET) scans are based on the use of positron emitting radionuclide tracers coupled to other molecules, such as glucose, ammonia, or water. The radionuclide tracers simultaneously emit 2 high-energy photons in opposite directions that can be simultaneously

detected (referred to as coincidence detection) by a PET scanner, consisting of multiple stationary detectors that encircle the area of interest.

A variety of tracers are used for PET scanning, including oxygen-15, nitrogen-13, carbon-11, and fluorine-18. The radiotracer most commonly used in oncology imaging has been fluorine-18, coupled with fluorodeoxyglucose (FDG), which has a metabolism related to glucose metabolism. FDG has been considered potentially useful in cancer imaging, since tumor cells show increased metabolism of glucose. This policy focuses on a specific indication for an oncologic application of PET scanning.

This policy focuses on the use of PET to determine early treatment response for cancer, that is, assessment of therapy response during cancer treatment. The purpose of the PET scan at this particular interval is to determine whether the treatment being given should be maintained or changed. Such a treatment strategy has been called “risk-adapted” or “response-adapted” treatment. This policy addresses detecting early response during short-term therapy, e.g., during cycle(s) of chemotherapeutic agents and/or a course of radiation therapy, and not on assessing response during use of long-term agents, such as tamoxifen.

This use is to be distinguished from all uses of PET in the initial diagnosis and staging of cancer and other uses after treatment, such as routine surveillance or detection of recurrence. This is also different from what has been called “response assessment” or “treatment response” in some reports but clearly refers to imaging done after completion of therapy for the purpose of prognosis and future treatment planning. Some reports differentiate between PET during treatment and PET after treatment by referring to PET during cancer treatment as “interim treatment response” or “interim staging” and PET at the conclusion of treatment as “restaging.”

The technique of using PET for early treatment response assessment involves comparing PET images before treatment and at some interval after the initial course of treatment. Many intervals have been used in various studies, and there appears to be no standard interval. Comparison of the pre-treatment and mid-treatment PET images can either be performed qualitatively or quantitatively. If a quantitative technique is used, a quantity called the standardized uptake value (SUV) is calculated for a specific region of the image. Various methods are used to compare the SUV between the 2 images, and a specific cut-off value is selected to determine whether the patient is responding or not responding to therapy. A change in SUV between 40% and 60% has often been used in studies of early treatment response.

POLICY

The use of positron emission tomography (PET) scans to determine early response to treatment (PET scans done during a planned course of chemotherapy and/or radiation) in patients with cancer is considered **experimental / investigational**.

RATIONALE

The use of positron emission tomography (PET) during treatment to detect early treatment response and as a trigger to potentially change treatment at that time makes this imaging procedure more closely tied to treatment than is usually the case with diagnostic tests, and thus,

risk-adapted treatment using PET could be evaluated in randomized clinical trials (RCTs). However, no such clinical trials have been completed, although at least 11 studies have been described in clinical trial registries. (1-11) Most of these registered RCTs address Hodgkin and non-Hodgkin lymphomas, although one trial includes patients with adenocarcinoma of the esophagus and gastroesophageal junction. Published case series, in which outcomes are reported for patients whose treatment has been directed by interim PET scans, appear to be rare. A comprehensive review of PET published by the National Health Service (NHS) in the United Kingdom in 2007 specifically looked for but did not find any studies reporting outcomes of patients whose treatment had been altered by interim PET. (12) However, according to a study generated from the National Oncologic PET Registry, which collected data on PET scans to develop evidence for Medicare coverage policy, PET is often used during treatment to change therapy, most often to a different therapy when the PET scan indicates progressive disease. (13) No patient outcomes were reported in this study, however.

The lack of studies showing impact on clinical outcomes based on PET-directed treatment makes it difficult to determine whether using PET during treatment will result in improved patient outcomes. Most studies that evaluate PET during treatment have analyzed PET in relation to various findings such as pathologic or clinical response at the end of treatment, PET at the end of treatment, or long-term results. Although associations between PET and all these findings have consistently been found for a number of cancers, whether such associations can lead directly to improved patient outcomes depends on the specific context of the treatment being used and the alternatives available. For example, if PET during treatment is highly specific for non-response to chemotherapy, and the alternative treatment for non-response is withdrawal of therapy, then treatment-directed PET could lead to withdrawal of ineffective treatment (and its adverse effects) for a subset of patients. If the alternative treatment is a different chemotherapeutic agent, then outcomes would be improved only if the alternative agent results in better outcomes. Use of PET during treatment may not improve outcomes compared to a PET performed after treatment or more than using a different method of response assessment. Interim PET could possibly simply advance the timing of alternative therapies, producing a lead-time bias effect without actually improving outcomes.

Other types of treatment protocols using PET-directed treatment that could potentially improve patient outcomes are possible. For example, treatment with less toxic agents that are less efficacious could be tried initially and changed quickly if PET showed that the initial agents were ineffective; thus allowing that subset of patients for whom a treatment is working to be treated successfully with less toxic treatment.

Evaluation of these types of treatment protocols would seem to require direct evidence from clinical trials, and conclusions about efficacy could not follow directly from current observational studies of PET. The following sections summarize the literature on PET during treatment for several major cancers in which its use has been proposed or is apparently being used.

Lymphoma

A 2007 National Comprehensive Cancer Network (NCCN) Task Force report on PET scanning in cancer makes no specific recommendation, but the language seems to indicate that the benefits of PET during treatment are not proven. (14) “Study results suggest that therapy does not need to be changed when the PET scan is negative, but a separate trial is needed to determine

whether a positive PET scan should prompt an alternative therapy and whether this alternative therapy can improve outcomes." A consensus statement released in 2007 by the Imaging Subcommittee of the International Harmonization Project in Lymphoma stated that use of PET for treatment monitoring during a course of therapy should only be done in a clinical trial or as part of a prospective registry. (15) This statement also comments on the need for clinical trials to demonstrate improved patient outcomes. The document otherwise proposes a strong endorsement for PET at the conclusion of therapy.

A comprehensive review of PET for lymphoma by the British National Health Service (NHS) identified 9 studies evaluating PET during treatment. (12) PET during treatment was highly associated with either patient survival or progression, such that patients who had positive PET scans during treatment were more likely to have progressed or have shorter survival. The 9 studies reviewed all had fewer than 100 patients, and different methods were used to analyze the PET scans. Cut-off values to differentiate a positive from a negative PET scan were invariably derived post hoc, possibly leading to an overestimate of discriminative capability.

In a case series of risk-adapted treatment using mid-treatment PET to alter therapy in lymphoma, 33 of 59 patients with positive mid-treatment PET scans had therapy changed to more aggressive therapy with platinum-based salvage chemotherapy, high-dose therapy, and autologous stem-cell transplantation. (16)These patients had a 2-year event-free survival of 67%, which is better than is historically associated with such patients who have positive mid-treatment PET scans. However, such case series data are not definitive in establishing the benefit of such a treatment strategy.

Some single-arm studies that assess outcomes of patients receiving treatment changes based on interim PET/CT (computed tomography) scans suggest that some chemotherapeutic regimens can be intensified or switched to less-toxic regimens without harm. (17, 18) The conclusions of single-arm studies may be biased by selection and lead-time bias. Imperfect prediction of poor prognosis may lead to some low-risk patients being classified as high risk, improving the group's survival. Earlier treatment using salvage therapies may result in a lead-time bias, which would also give an apparent survival improvement. Given the potential for selection and lead-time biases, comparative trials would be necessary to determine the efficacy of such a strategy.

In the 2013 update of the NCCN guidelines on Hodgkin lymphoma, several statements were made regarding use of interim PET. (19) Initial studies suggested that for early stage Hodgkin lymphoma (stage I to II favorable disease), interim PET imaging was not considered to be of important prognostic significance. However, the guideline cites two prospective 2012 studies by Kostakaglu et al. and Zinzani et al. that found that PET scans after 2 cycles of chemotherapy were significant predictors of progression-free survival. (20, 21) For more advanced disease, interim PET imaging predicts long-term outcomes. Although interim PET has prognostic capability, the document states that "guiding therapy based on the results of interim PET imaging is considered investigational and is not recommended outside the context of a clinical trial." However, if interim PET imaging is to be performed in patients with stage I to II unfavorable (bulky or nonbulky) disease or stage III to IV disease, it may be performed after 2 to 4 cycles of chemotherapy. Interim staging with diagnostic CT was recommended for certain patients receiving certain treatment regimens. For non-Hodgkin lymphoma, the most recent 2013 NCCN guidelines do not support interim PET for altering treatment. (22)

Lung Cancer

The NCCN Task Force report discusses studies examining the role of PET in determining early treatment response for non-small-cell lung cancer but makes no statement recommending such use. (14) Three studies were cited that showed that interim PET scans during neoadjuvant therapy were associated with pathologic findings at surgery or with median time to cancer progression.

No studies were identified that evaluated the outcomes of patients whose treatments were altered with mid-treatment PET. The British NHS review identified several studies that evaluated use of PET for post-treatment assessment and only one study that evaluated PET during treatment. (12) In that study, PET findings during chemotherapy were associated with clinical measures of best response evaluated at the end of therapy with a sensitivity of 95% and a specificity of 74%. Other studies have shown an association between PET and overall survival in patients. However, early prediction of survival does not translate to patient benefit unless the decisions that were based on those predictions can result in improved patient outcomes by either extending survival or improving quality of life.

Ovarian Cancer

Ovarian cancer was the most common type of cancer in which PET was used during treatment in the National Oncologic PET registry. (13) Neither the NCCN Task Force nor the British NHS review included ovarian cancer among the uses of PET considered in their reports. (12, 14)

There were no case series or comparative trials of risk-adapted treatment for ovarian cancer identified. One study evaluates the use of PET during chemotherapy to predict patient outcomes in 33 patients, without making management changes. (23) Using various thresholds of change in standardized uptake value (SUV), median survival was worse among those who had less of a change in SUV. For example, at a threshold of decrease in SUV of 20% after the first cycle of chemotherapy, overall survival was 38.3 months in responders and 23.1 months in nonresponders. Clinical response, CA-125 response, and histopathologic response did not correlate with overall survival. Although PET during treatment appears to be associated with response and may be better than other methods of prognosis, whether such improved prediction leads to improved patient outcomes is not demonstrated in this type of study.

Other Cancers

Other cancers were assessed for PET during treatment in the NCCN Task Force Report. (14) The report cites 1 small study of colorectal cancer patients showing an association between PET and tumor response to 5-fluorouracil after 1 month of therapy. They concluded in their summary recommendation that PET scans are not routinely indicated to monitor response to chemotherapy or radiation therapy. The report cited several studies of breast cancer patients and early PET and commented on promising data but included this indication among several other uses in breast cancer that are in need of further research.

Other cancers were also assessed for PET during treatment in the British NHS review. (12) The report identified a prior systematic review and 3 other primary studies that demonstrated associations between PET during treatment and responses in breast cancer. No studies showing outcomes of PET-directed treatment for breast cancer were identified. For colorectal cancer, 1

study was identified that showed that PET after 1 month of chemotherapy predicted outcome, but the predictive accuracy was rather low. For head and neck cancer, esophageal cancer, and melanoma, only studies that evaluated PET performed after treatments were identified.

Including sections of this report summarized in other sections of this policy, the British NHS review found 22 studies of PET during treatment. They conclude that many of the studies were small, evaluating different treatments, with a diversity of response targets and monitoring methods. There was little evidence of change in patient management, even anecdotally, and no published evidence of successful applications to drug development.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from one physician specialty society and 5 academic medical centers while this policy was under review in 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. In general, there was agreement with the conclusions of this policy from those providing input. Most of the disagreement related to use of PET scans during a planned course of treatment for patients with Hodgkin lymphoma. Some reviewers felt current data were sufficient to show benefit, others commented that additional studies needed to evaluate this issue.

Summary

There is a lack of high-quality literature on the use of positron emission tomography (PET) scans in various cancers to determine early response to treatment. These scans may provide some additional information on risk prediction and/or prognosis, but the effect of these scans on the net health outcome is not known. Comparative trials would be necessary to determine if health outcomes are improved based on treatment changes instituted based on early PET scans. Therefore, PET scanning done during a planned course of cancer treatment for the purpose of altering the treatment plan is considered investigational.

Practice Guidelines and Position Statements

A 2007 National Comprehensive Cancer Network (NCCN) Task Force report on PET scanning in cancer makes no specific recommendation, but the language seems to indicate that the benefits of PET during treatment are not proven. (14) “Study results suggest that therapy does not need to be changed when the PET scan is negative, but a separate trial is needed to determine whether a positive PET scan should prompt an alternative therapy and whether this alternative therapy can improve outcomes.” A consensus statement released in 2007 by the Imaging Subcommittee of the International Harmonization Project in Lymphoma stated that use of PET for treatment monitoring during a course of therapy should only be done in a clinical trial or as part of a prospective registry. (15) This statement also comments on the need for clinical trials to demonstrate improved patient outcomes. The document otherwise proposes a strong endorsement for PET at the conclusion of therapy

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

78811	Positron emission tomography (PET) imaging; limited are (eg, chest, head/neck)
78812	Positron emission tomography (PET) imaging; skull base to mid-thigh
78813	Positron emission tomography (PET) imaging; whole body
78814	Positron emissio tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (eg., chest, head/neck)
78815	Positron emissio tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
78816	Positron emissio tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body

DIAGNOSES

Experimental / Investigational on all diagnoses related to this medical policy.

REVISIONS

10-16-2013	PET Scanning in Oncology to Detect Early Response during Treatment was originally part of the Positron Emission Tomography (PET) medical policy. This portion was pulled out and placed into a separate medical policy, Positron Emission Tomography (PET) Scanning: In Oncology to Detect Early Response during Treatment.

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